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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
07/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/558,155	WAKITA ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 14-23* is/are pending in the application.

4a) Of the above claim(s) *4 and 14-20* is/are withdrawn from consideration.

5)☒ Claim(s) *23* is/are allowed.

6)☒ Claim(s) *1-3,5-9,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/9/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response dated March 9, 2009, to the non-final action dated December 8, 2008 has been entered. Claims 1, 3 and 5 have been amended; claims 10-13 cancelled and claims 22 and 23 newly added. Accordingly, claims 1-9 and 14-23 are pending in the application. Claims 4 and 14-20 stand withdrawn from further consideration, with traverse, as drawn to non-elected inventions and species of the invention. The claims have been examined commensurate in scope with the elected invention, and the species of the invention, i.e. a replicon RNA, comprising a nucleotide sequence containing at least the 5' untranslated region, the nucleotide sequence encoding NS3 protein, NS4A protein, NS4B protein, NS5A protein and NS5B protein and the 3' untranslated region on the genomic RNA of hepatitis C virus (HCV) of genotype 2a, and a replicon-replicating cell comprising said replicon RNA, together with SEQ ID NO: 1 as the replicon RNA, SEQ ID NO:9 as the 5' untranslated region, and SEQ ID NO: 11, as the 3' untranslated region; and the species of neomycin resistance gene, human liver derived cell, Huh7 cell and replicon RNA mutation (b).

Claims 1-3, 5-9 and 21-23 are under current examination.

Examiner's Note

The previous Office action dated December 8, 2008 contained errors regarding claim 21, that included designating the claim as rejected in the Office action summary form and indicating the claim as considered allowable in the conclusion of the Office action. Claim 21 is subject to a new ground of rejection as set forth below. Thus, this Office action has been made non-final.

The prior art of record does not appear to teach or suggest an HCV genotype 2a RNA replicon comprising the nucleotide sequence of SEQ ID NO: 1.

Information Disclosure Statement

The information disclosure statement filed March 9, 2009 is in compliance with 37 CFR 1.98(a)(2). Thus, the information referred to therein has been considered, and indicated as such on Applicants' IDS form.

Withdrawn Claim Objection

Claim 5 was objected for improperly combining "or" with "and" with regard to parts (a) and (b). Applicants have amended the claim, obviating the ground for objection. Thus, the objection is hereby withdrawn.

New Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5, 21 and 22 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 5 and 21 are unclear. The claims recite nucleotide sequences "represented by" SEQ ID NOS: 1, 9 and 11. To represent may be defined as "to serve as a specimen, example, or instance of" (Merriam-Webster Online Dictionary). MPEP 2173.05(d) indicates that exemplary language in the claim may lead to confusion over the intended scope of a claim. In the instant case the representation may be a primer or an oligonucleotide corresponding to only a portion of the sequences. Thus, the metes and bounds of the claim are not clearly set forth. The rejection may be obviated by substituting "as set forth in" for "represented by".

Claim 22 is unclear. The claim recites a first nucleic acid comprising a regulatory region that causes transcription or translation. However, the object of said transcription or translation remains undefined. The claim is further unclear with regards to a single regulatory region "causing" transcription or translation. Figure 1 of the specification depicts a T7 promoter as the

first nucleic acid operably linked to a neo gene, that together constitute heterologous sequences; though it is unclear how a transcription promoter can cause translation. Further, the IRES separately depicted in the Figure cannot constitute the single regulatory region, as it simply directs translation, and not transcription.

Withdrawn Claim Rejections - 35 USC § 102

Claim 1 was rejected under 35 U.S.C. 102(b) as being anticipated by Kato et al. (J. Med. Virol. 64:334-339; 2001), in the previous Office action dated December 8, 2008. Applicants have amended the claim, introducing the limitation for a subgenomic RNA derived from HCV, not taught by Kato et al. Thus, the rejection is hereby withdrawn.

Maintained & New Claim Rejections - 35 USC § 103

Claims 1, 2 and 6-9 stand rejected and claim 22 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Ikeda et al. (J. Virol. 76:2997-3006; 2002), in view of Kato et al. (J. Med. Virol. 64:334-339; 2001). Applicants' cancellation of claims 10-13 renders their rejections moot. The rejection set forth on pp. 4-6 of the previous Office action dated December 8, 2008 is maintained for claims 1, 2 and 6-9, and further applied to new claim 22 for reasons of record.

The claims embrace a replicon RNA, comprising a nucleotide sequence containing at least the 5' untranslated region, the nucleotide sequence encoding NS3 protein, NS4A protein, NS4B protein, NS5A protein and NS5B protein and the 3' untranslated region of the genomic RNA of hepatitis C virus of genotype 2a, further containing a neo selection marker and at least one IRES sequence, and a nucleic acid construct comprising a heterologous regulatory region operably linked thereto.

Ikeda et al. describe selectable subgenomic RNAs derived from an infectious molecular clone of the HCV-N strain of HCV that are capable of efficient self-replication in cultured human hepatocyte cell line Huh7, with selection for G418 resistance following transfection (Title and Abstract). The authors depict clones containing a 5'UTR, Neo gene, EMCV IRES, NS3, NS4A, NS4B, NS5A, NS5B and 3'UTR regions (Fig. 1, p. 2998). Ikeda et al. further describe the construction of plasmids with a T7 transcriptional unit operably linked to the neo gene and

containing the sequence of a candidate replicon (second column, p. 2999; limitation of claim 22).

While the HCV-N strain described by Ikeda et al. is a genotype 1b virus, HCV genotype 2a virus was characterized in the prior art, as evidenced by Kato et al., who describe the recovery, cloning and sequence analysis of HCV type 2a genome from a hepatitis patient (Abstract). The HCV isolate contained the 5'UTR, NS3, NS4A, NS4B, NS5A, NS5B and 3'UTR regions (Table 1, p. 337).

The teachings of Ikeda et al. and Kato et al. are both directed to the characterization of HCV replicon RNA sequences. Thus a person of ordinary skill in the art would have been motivated to combine their respective teachings and construct subgenomic clones of the HCV 2a genotype, in the manner prescribed by Ikeda et al.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention, to produce subgenomic clones of HCV genotype 2a as applied to the genotype 1b of Ikeda et al., resulting in the replicon RNA of the instantly claimed invention. A person of ordinary skill in the art would have been motivated to combine the respective teachings of Ikeda et al. and Kato et al. to produce subgenomic RNA of genotype 2a, because such would allow the production of HCV 2a clones, for analysis and characterization of replication competence, with a reasonable expectation of success.

Response to Arguments

Applicants argue that Ikeda et al. neither describe nor suggest a reasonable expectation of success in obtaining self-replicable subgenomic RNAs derived from an HCV strain of genotype 2a, because while Ikeda et al. describe the production of self-replicable subgenomic RNAs derived from the HCV-N strain of HCV genotype lb, they state, only HCV replicons derived from a single, genotype lb strain of HCV, Conl, have been shown previously to be replication competent, and efforts to derive replication-competent, subgenomic RNAs from known infectious cDNAs of the genotype la, H77C virus (13, 25), have proven unsuccessful. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that the only strain indicated by Ikeda et al. as being problematic is a genotype la, H77C virus, and not the instantly claimed genotype 2a strain. Ikeda

et al. state: "Previous studies have demonstrated that subgenomic RNA replicons derived from diverse members of the family of *Flaviridiae* are capable of autonomous replication in permissive cell lines…Recent reports make it evident that analogous subgenomic HCV replicons are also capable of replication in Huh7 cells…Here, we describe the replication competence of subgenomic RNAs that are derived from a second, completely independent HCV isolate, HCV-N" (first column, p. 3004). Thus, a person of ordinary skill in the art, reading the teachings of Ikeda et al. in full context would be apprised that various replication competent HCV strains have been successfully constructed. As stated in MPEP 2143.02, obviousness requires only a reasonable expectation of success.

Applicants' arguments with regard to the post-filing reference of Blight et al. are not found persuasive, because the reference is not one considered by a person of ordinary skill in the art at the time the invention was made. MPEP 2141 II. Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). Further, the reference is silent with regards to HCV genotype 2a instantly claimed.

Thus, the rejection is maintained for claims 1, 2 and 6-9, and further applied to new claim 22 for reasons of record and the foregoing discussion.

Claim 3 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Ikeda et al. (J. Virol. 76:2997-3006; 2002), in view of Kato et al. (J. Med. Virol. 64:334-339; 2001), as applied to claims 1, 2, 6-9 and 22 above, and further in view of JP 2002-171978 (Published June 18, 2002). The rejection set forth on pp. 6-7 of the previous Office action dated December 8, 2008 is maintained for reasons of record.

The claims embrace a replicon RNA, comprising a nucleotide sequence containing the 5' untranslated region (SEQ ID NO: 9), the nucleotide sequence encoding NS3 protein, NS4A protein, NS4B protein, NS5A protein and NS5B protein and the 3' untranslated region of the genomic RNA (SEQ ID NO: 11) of JFH-1 strain of hepatitis C virus of genotype 2a, further containing a neo selection marker and an IRES sequence.

Ikeda et al. describe selectable subgenomic RNAs derived from an infectious molecular clone of the HCV-N strain of HCV that are capable of efficient self-replication in cultured human hepatocyte cell line Huh7, with selection for G418 resistance following transfection (Title and Abstract). The authors depict clones containing a 5'UTR, Neo gene, EMCV IRES, NS3, NS4A, NS4B, NS5A, NS5B and 3'UTR regions (Fig. 1, p. 2998).

Kato et al. describe the recovery, cloning and sequence analysis of HCV type 2a (JFH-1 strain) genome from a hepatitis patient (Abstract and second column, p. 334).

The HCV 5' and 3' UTR sequences as represented by SEQ ID NOS: 9 and 11, respectively, were disclosed in Sequence 1 of JP 2002-171978 corresponding to HCV type 2a (JFH-1).

The teachings of Ikeda et al., Kato et al. and JP 2002-171978 are all directed to the characterization of HCV replicon RNA sequences. Thus a person of ordinary skill in the art would have been motivated to combine their respective teachings and construct subgenomic clones of the HCV 2a genotype comprising SEQ ID NOS: 9 and 11.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention, to produce subgenomic clones of HCV genotype 2a comprising the sequences disclosed in JP 2002-171978, resulting in the method of the instantly claimed invention. A person of ordinary skill in the art would have been motivated to combine the respective teachings of Ikeda et al. Kato et al. and JP 2002-171978 to produce subgenomic RNA of genotype 2a, because such would allow the production of HCV 2a clones, for analysis and characterization of replication competence, with a reasonable expectation of success.

Response to Arguments

Applicants argue that the same arguments with regards to Ikeda et al. and Kato et al. apply to claim 3 and the disclosure of Sequence 1 in JP 2002-171978 fails to overcome the negative teachings and lack of expectation of success. Applicants' arguments have been fully considered, but are not found persuasive. Applicants are directed to the response provided above. Thus, the rejection of claim 3 is maintained for reasons of record and the commentary set forth above.

Conclusion

Claims 1-3, 5-9, 21 and 22 are not allowed.

Claim 23 is considered allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633